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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/986,344	11/08/2001	Peter K. Law	37794-0032	5167

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EXAMINER	
SHUKLA, RAM R	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 06/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/986,344	LAW, PETER K.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1-15-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of the invention of group I, drawn to a method of in vivo delivery of a peptide that binds to opioid receptor in Paper filed 3-8-04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. The invention of claims 33-51 drawn to a method of in vivo delivery of a peptide that interferes with binding of substance P to its receptor is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Election was made **without** traverse in Paper filed 3-8-04.

3. Claims 33-51 are objected because they recite non-elected invention. Appropriate correction is required.

Information Disclosure Statement

4. It is noted that the IDS submitted on 1/15/03 lists only six references however twelve references were provided with the application when filed or when IDS was filed. It is noted that those references that were not listed on the 1449 have not been considered. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office. Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 33-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 33 and 42 recite "obtaining allogeneic muscle cells from a patient" and then introducing the cells to the patient. It is unclear as to how a patient's own cells could be allogeneic to self.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 33-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al (The Journal of Neuroscience 14:4805-4814, 1994) in view of Beutler et al (Journal of Neurochemistry 64:475-481, 1995), Deglon et al (Human Gene Therapy 7:2135-2146, 1996), Law (WO 96/18303, 1996), , Law et al (Cell Transplantation 2:485-505, 1993), Allen and Rankin (Proceedings of the Experimental Biology and Medicine 194:81-86, 1990) and Morris and Herz (Naunyn Schmiedebergs Arch Pharmacol 336:240-243, 1987 (abstract only).

Claimed invention encompasses a method for supplying the central nervous system of a patient a peptide that binds to an opioid receptor comprising obtaining allogeneic muscle cells from the patient, preparing an in vitro culture, transducing the culture with DNA encoding the peptide such that the cells express the peptide, introducing the cells as a suspension to a muscle that is selected from a list. Dependent claims recite stimulation of patient's skeletal muscle by different methods, amount of cells produced, and treating the cells with growth factors before administration to the patient in a muscle or fat cells.

Wu et al teaches implantation of genetically modified cells expressing beta-endorphin in mouse spinal cord for producing aninociception (see the abstract). The art reviews the state of the art of pain treatment by administering a patient peptides (such as enkephalin and beta-endorphin) that bind to opioid receptors (see the introduction). The art also teaches the use of the chronic implantation of opioid secreting cells as an approach for studying opioid tolerance (see the introduction section on page 4806). The art does not teach administration of myoblasts expressing a peptide that binds to opioid receptor to a muscle for treating pain.

Beutler et al teaches expression of an opioid receptor in primary fibroblasts for using peptides in gene therapy and for obtaining beta-endorphin secreting cells for pain treatment. The art teaches retroviral vector expressing beta-endorphin, cell culture, transduction of cells, characterization of cells for secretion of the beta-endorphin and the activity of the secreted beta-endorphin for binding to opioid receptors (see the methods section on page 476, figure 1). The art also teaches that beta-endorphin has been used in animals and humans by intrathecally administration. The art also teaches applicability of intrathecal grafting of beta-endorphin secreting fibroblasts for treatment of pain and the problems associated with the method and that there may be need to modification of the strategy to achieve a gene therapy for chronic pain (see the last full paragraph in the discussion section on page 480). The art does not teach administration of myoblasts expressing a peptide that binds to opioid receptor to a muscle for treating pain.

At the time of the invention, it was routine to use myoblasts for ex vivo gene therapy for treating diseases and providing recombinant therapeutic proteins in an animal. For example, Deglon et al teach delivery of recombinant ciliary neurotrophic factor to central nervous system by administering differentiated myoblasts. This art teaches intrathecal administration of the cells in a capsule to deliver the neurotrophic factor behind the blood brain barrier, culture conditions for myoblasts, differentiation protocol, transduction with a vector, encapsulation of 108 cells per ml and intrathecal administration of the encapsulated cells (see the methods section). The cells survived in the CSF for over three months and

produced CNTF. The authors concluded that myoblasts could be used fro long-term delivery of recombinant proteins in the treatment of diseases (see the last paragraph on page 2144). Law (1996) teaches myoblast therapy for mammalian diseases using myoblasts, and or their physical, genetic and chemical derivatives. The art teaches method of isolating, culturing, transducing and administration of the myoblasts (see the claims and the rest of the article). The art also teaches an automated cell processor which can be used to manufacture, at a single run, large quantities (greater than 100 billion) of normal or genotypically or phenotypically altered myogenic cells (see the abstract of the prior art). This prior art further teaches that large chondroitin-6-sulfate proteoglycan (LC6SP) stimulates myoblast proliferation and that the use of LC6SP (ranging from approximately 5 micro molar to about 5 mM) in the transfer medium will likely lead to greater myogenic transfer therapy success. It further teaches that insulin also facilitates the developmental process of myoblasts and may result in the formation of myotubes soon after myoblast injection (see lines 22-31 on page 20). The art also teaches to inject the cells at such angle so as to achieve maximum cell fusion with the least number of injections (see page 14, lines 1-10). The art of record, at the time of the invention, also taught administering 5 billion cells to a patient for treating a disease (see Law et al 1993).

At the time of the invention, it would have been obvious to one of ordinary skill in the art, to modify the methods of Wu et al and Beutler et al to use myoblasts for providing opioid peptides to animals for therapy of pain. An artisan could isolate a patient's myoblasts, transduce them with a retroviral vector expressing an opioid peptide, culture the cells in large quantity and administer transduced cells to the patient in a muscle near the spinal cord where there are opioid receptors with a reasonable expectation of success since in view of the teachings of the prior arts, such as those of Deglon et al or Law. An artisan would have been motivated to use a patient's own myoblasts for expressing opioid peptide for treating pain because cells expressing opioids such as endorphin or enkephalin were known to be used in the art and because of the cells coming from the patient would not require any immunosuppressive intervention. Furthermore an artisan

would have been motivated to administer large chondroitin-6-sulfate proteoglycan and insulin to patients with the myogenic cells because these agents would have increased the proliferation and fusion of the myoblasts to muscle fibers and formation of myotubes.

Regarding claims that recite mechanical stimulation of the patients skeletal muscle tissue to produce a reservoir of satellite myoblast cells, it is noted that at the time of the invention, the art of Allen and Rankin (1990) taught that satellite cells are myogenic cells attributed with the role of postnatal growth and regeneration in skeletal muscle. These cells help in fiber growth and repair because following proliferation and differentiation, these cells fuse with one another or with adjacent muscle fibers. The prior art further teaches that several factors, such as exercise, trauma, passive stretch, innervation, and soluble growth factors, affect the proliferation and subsequent differentiation of satellites (see abstract on page 81). Therefore, in view of the teachings of the art an artisan would have stimulated the microenvironment of a patient's muscles to increase the yield of satellite cells with a reasonable expectation of success. An artisan would have been motivated to do so because the said process would have increased the fusion potential of the satellite cells and therefore would have increased the efficacy of the gene therapy approach. In regard to particular muscles recited in the claims, it is noted that an artisan would have targeted (chosen) muscles affected with pain or muscles that would have allowed closer proximity to spinal cord such as neck muscles or paraspinal muscle and levator scapulae muscles for injecting genetically engineered myoblasts to maximize the efficacy of the therapy. Additionally, such sites have a higher concentration of opioid receptors (see the abstract of Morris and Herz 1987).

9. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (571) 272-0735 . The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are

unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. The fax phone number for TC 1600 is (703) 872-9306. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (571) 272-0532.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ram R. Shukla, Ph.D.
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Art Unit 1632

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER